Summary of Major Literature Related to COVID-19 (Week of March 22–29)

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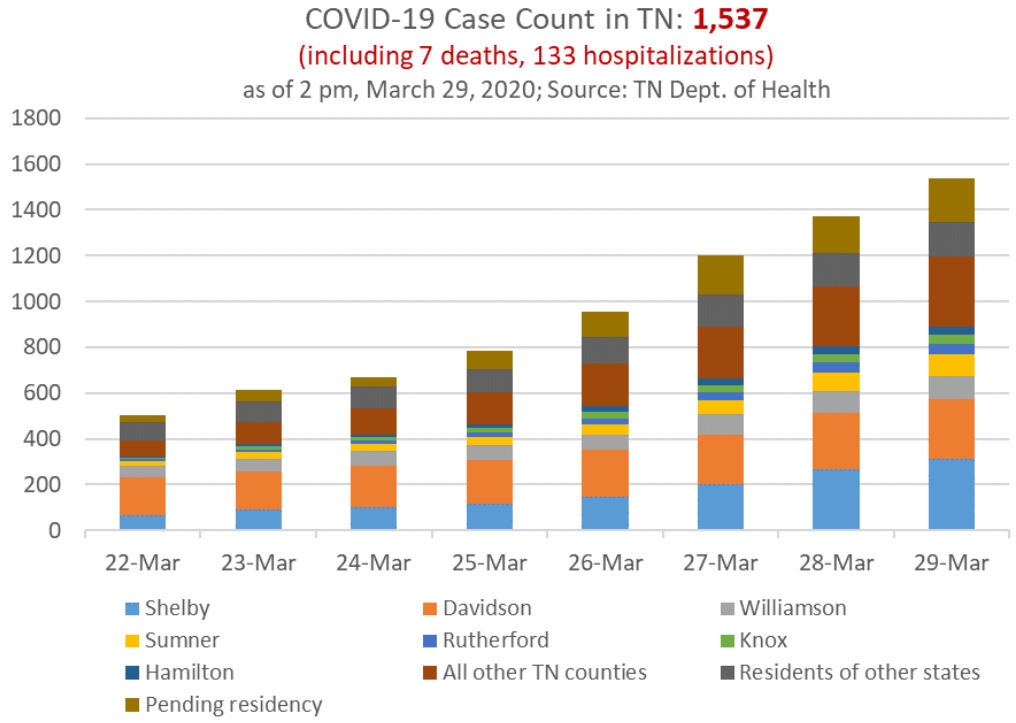
***This is informational and not intended to create variance from VUMC policies/guidance.**

EPIDEMIOLOGY

Tennessee and Nashville



- Total TN cases = 1,537
- Seven TN counties have over 30 cases
- Top three counties:
  - Shelby = 313
  - Davidson = 260
  - Williamson = 101
- By age:

Age group	Cases	%
0–10	17	1.1%
11–20	80	5.2%
21–30	380	24.7%
31–40	239	15.5%
41–50	262	17.0%
51–60	176	11.5%
61–70	97	6.3%
71–80	33	2.1%
80+	14	0.9%

- Ages 21-50 make up 57% of cases in TN

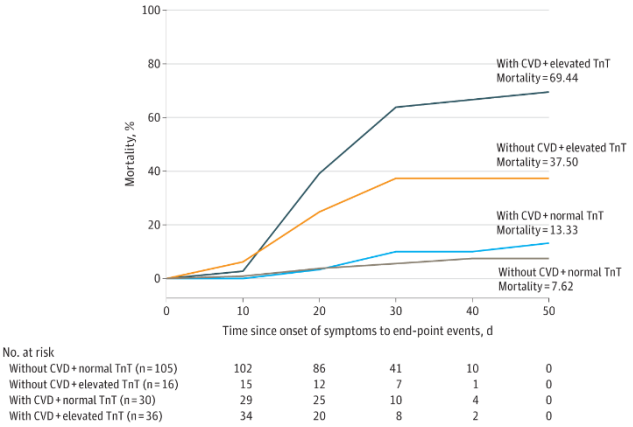
Comorbidities/prognostic factors

1. **Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.** Zhou et al. Lancet. March 1, 2020. https://doi.org/10.1016/S0140-6736(20)30566-3

- Comorbidities such as hypertension, diabetes and coronary heart disease are consistently associated with increased mortality in COVID-19, but potential for confounding by age and other factors needs to be considered
- Retrospective two-hospital EMR study of all 191 adult COVID-19 inpatients
- Elevated (>28 pg/ml) high-sensitivity cardiac troponin I and occurrence of acute cardiac injury or acute kidney injury strongly associated with death
- In multivariable models, strongest predictors of death: older age, higher Sequential Organ Failure Assessment (SOFA) score, and d-dimer (marker of coagulation activity) > 1 µg/mL at admission
- Limitations: unrepresentative sample and incomplete follow-up

2. **Cardiovascular implications of fatal outcomes of patients with Coronavirus Disease 2019.** Guo et al. JAMA Cardiol. March 27, 2020. https://jamanetwork.com/journals/jamacardiology/fullarticle/2763845

- Study of 187 inpatients, 144 discharged and 43 died



- 35% had underlying CVD (hypertension, CVD, cardiomyopathy) and 28% had elevated troponin T (TnT), indicating myocardial injury
- Myocardial injury was associated with markedly increased risk of death (see Figure)
- Highest mortality (69%) in those with both underlying CVD and elevated TnT
- Lowest mortality in those without CVD or elevated TnT (7.62%)
- Mortality was relatively favorable (13%) in patients with underlying CVD but no myocardial injury

- Myocardial injury is associated with escalation of proBNP and arrhythmias
- Plasma TnT and proBNP increased significantly from admission in those who died
- "Aggressive treatment may be considered for patients at high risk for myocardial injury"

3. **Kidney disease is associated with in-hospital death of patients with COVID-19.** Cheng et al. Kidney Int. March 19, 2020. https://doi.org/10.1016/j.kint.2020.03.005
The Novel Coronavirus 2019 epidemic and kidneys (Review article). Naicker et al. Kidney Int. March 7, 2020. doi: 10.1016/j.kint.2020.03.001.

- High frequency of renal abnormalities among 710 consecutive hospitalized patients with COVID-19:
  - Proteinuria (44%) and hematuria (27%) on admission
  - Elevated serum creatinine (14%), elevated blood urea nitrogen (13%) and estimated glomerular filtration under 60 ml/min/1.73m^2 (13%)
  - Acute kidney injury (AKI) occurred in 5.1% of patients
- All of these renal abnormalities were strong independent risk factors for in-hospital death in multivariable models
- Mechanisms of kidney involvement are unclear but possibly include sepsis leading to cytokine storm syndrome or direct cellular injury due to SARS-CoV-2

Case fatality

4. **Case-Fatality rate and characteristics of patients dying in relation to COVID-19 in Italy.** Onder et al. JAMA. March 23, 2020. https://jamanetwork.com/journals/jama/fullarticle/2763667

- Case fatality rate in Italy is 7.2% (1625 deaths/22 512 cases, March 17), substantially higher than China (2.3%)
- Potential explanations for higher case fatality in Italy:
  - Older patient population
  - Inclusion of deaths from preexisting disease (non-COVID-19–related)
  - Prioritized testing of patients with more severe clinical symptoms and required hospitalization

CLINICAL SYMPTOMS

5. **Luo S, Zhang X, Xu H. Don't overlook digestive symptoms in patients with 2019 novel coronavirus disease (COVID-19).** Luo et al. Clin Gastroenterol Hepatol. March 20, 2020**.** doi.org/10.1016/j.cgh.2020.03.043

- Data from 1141 cases admitted to a Wuhan hospital showed 16% whose initial symptoms were predominantly gastrointestinal; most common GI symptoms were loss of appetite (98%), nausea (73%), vomiting (65%), and diarrhea (25%).
- Patients also presented low leukocyte and lymphocyte and elevated C-reactive protein.

6. **Anosmia, hyposmia, and dysgeusia symptoms of Coronavirus Disease.** Report of the American Academy of Otolaryngology – Head and Neck Surgery. March 22, 2020. https://www.entnet.org/content/coronavirus-disease-2019-resources
- Loss of or altered sense of smell or taste could be an early symptom for COVID-19 patients
- Data from South Korea suggest that 30% of patients testing positive have had anosmia as their major presenting symptom in otherwise mild cases.

TREATMENT

7. **COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers: What is the evidence?** Patel and Verma. JAMA. March 24, 2020. https://jamanetwork.com/journals/jama/fullarticle/2763803
HFSA/ACC/AHA statement addresses concerns re: using RAAS antagonists in COVID-19. Accessed March 2, 2020. https://professional.heart.org/professional/ScienceNews/UCM_505836_HFSAACCAHA-statement-addresses-concerns-re-using-RAAS-antagonists-in-COVID-19.jsp
- Human angiotensin-converting enzyme 2 receptor (ACE2) serves as entry point for SARS-CoV-2 infection
- Potential upregulation of ACE2 by ACEIs or ARBs generated speculation of increased COVID-19 susceptibility or mortality in patients taking these medications (see "PATHOPHYSIOLOGY" below)
- No experimental or clinical evidence is currently available that treatment with ACEIs or ARBs is associated with beneficial or harmful outcomes in COVID-19
- **HFSA/ACC/AHA and Council on Hypertension of the European Society of Cardiology:** Patients should continue ACEI and ARB therapy as prescribed

8. **The Cancer Letter Special Report**. **Class of drugs used to treat CAR T-cell toxicity may reduce COVID-19 deaths.** Mar. 24, 2020. https://cancerletter.com/articles/20200324_1/
- A class of drugs that has been used to treat adverse events associated with CAR T-cell therapy is emerging as a potential treatment for COVID-19.
- The available drugs, both interleukin-6 receptor antagonists, have the capacity to treat the cytokine release syndrome, sometimes also known as the cytokine storm syndrome, a large, rapid release of cytokines into the blood as a result of viral infections or immunotherapy
- The drugs—two of which are now being rushed into late-stage clinical trials—are approved by FDA for rheumatology indications: Actemra (tocilizumab, Genentech), Kevzara (sarilumab, Regeneron Pharmaceuticals and Sanofi) and Sylvant (siltuximab, EUSA Pharma)
- The hypothesis that blocking IL-6 would stop the overactive inflammatory response in the lungs of patients who are severely ill with COVID-19 is based on preliminary data from a 20-patient single-arm study in China using tocilizumab. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. Xu et al. https://www.ser.es/wp-content/uploads/2020/03/TCZ-and-COVID-19.pdf

9. **Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma.** Shen et al. JAMA. March 27, 2020. https://jamanetwork.com/journals/jama/fullarticle/2763983
- Prior experience with convalescent plasma effective with SAES-CoV, H5N1 avian influenza, & H1N1 influenza

- 5 critically ill patients with COVID-19, ARDS, & increasing viral load despite antiviral treated with convalescent plasma from donors with high SARS COV-2 specific and neutralizing Ab titers
- Clinical improvement observed (fever resolution, viral load clearance, ARDS resolution) and 3 patients discharged from hospital
- Limitations: small case series, no controls

CLINICAL MANAGEMENT

10. **Novel 2019 coronavirus SARS-CoV-2 (COVID-19): An updated overview for emergency clinicians.** Giwa et al. Emerg Med Pract. March 23, 2020**.** **https://www.ebmedicine.net/topics/infectious-disease/COVID-19**
    This comprehensive overview draws from early research and clinical experiences in Italy and offers valuable links to reliable and trustworthy up to date resources
    Some key points:

- Doffing of PPE is often the highest-risk procedure during the patient-physician interaction
- Non-invasive ventilation is a powerful tool to buy some time until an ICU bed becomes available
- Lung ultrasound is valuable for evaluating patients on arrival, more sensitive than chest xray
- Management options: antivirals, glucocorticoids, and novel treatments to manage cytokine storm
- Airway management options: NIV, helmet CPAP, and filters
- Steps for rapid sequence intubation in the ED and managing disaster ventilation
- Prepare psychological support for the staff early
- New information on managing pediatric and pregnant patients

BIOLOGY/PATHOPHYSIOLOGY

11. **Angiotensin Converting Enzyme 2: A Double-Edged Sword.** Wang et al. Circulation. https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.120.047049
    Renin-Angiotensin System Blockers and the COVID-19 Pandemic: At Present There Is No Evidence to Abandon Renin-Angiotensin System Blockers . Danser et al. Hypertension. https://www.ahajournals.org/doi/pdf/10.1161/HYPERTENSIONAHA.120.15082
    Is There an Association Between COVID-19 Mortality and the Renin-Angiotensin System-a Call for Epidemiologic Investigations. Hanff et al. Clin Infect Dis. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa329/5811880

- There is conflicting mechanistic evidence for the association between renin-angiotensin system (RAS) inhibition and COVID-19 mortality; this is a "key clinical research priority"
- ACE2 (angiotensin-converting enzyme 2) is the receptor that allows coronavirus entry into cells
- ACE inhibitors do not inhibit ACE2, but angiotensin II type 1 receptor blockers (ARBs) and cardiovascular disease have been suggested to upregulate ACE2 which may increase the virulence of SARS-CoV-2 within the lung and heart
- Conversely, mechanistic evidence from related coronaviruses suggests that SARS-CoV-2 infection may downregulate ACE2, leading to toxic over-accumulation of Angiotensin II that induces acute respiratory distress syndrome and fulminant myocarditis; it is unclear whether RAS inhibition could mitigate this effect
- There are no data supporting that ACE inhibitors or ARBs facilitate coronavirus entry by increasing ACE2 expression
- Animal data suggest potential beneficial pulmonary and cardiovascular effects of elevated ACE2 expression